Biological Laboratory
Cold Spring Harbor
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Dear Haldane:

I am returning herewith your manuscript together with a typewritten copy of it. This was made by a student and I apologize that it is not reliable. The algebra was over his head and he misread some of your formulas. I have caught some of these but probably not all.

Your manuscript has been read by Luria, Hershey, and several others and I gave a talk about it here last week which was attended by those who took the phage course this year and by a few outsiders, mostly people to whom algebra is more strange than Chinese.

I am also enclosing a reprint of a little note on this problem which I published in the J. of the Tenn. Acad. of Sc., which has not yet found, to my knowledge, a sympathetic reader.

I have a few comments on your paper and will arrange these as footnotes to the type written copy which is marked correspondingly.

1. When we estimated the mutation rate from the mean number of mutants we took as the theoretical mean not the true mean of an infinite series of tests but the likely mean to be expected in a limited number of tests. The discrepancies between the two methods of estimation of the mutation rate can not be explained in the way you suggest.

2. I obtain $p_0 = e^{-2g}\,(1+2g(1-2g)N^{-1} + \ldots)$

$$p_1 = ge^{-2g}\,(1+2g(2-2g)N^{-1} + \ldots)$$

3. I do think think this recurrence formula does not check within the preceding line. I obtain instead

$$2^{-n-1}u_{n+1} - 1 = (1-m/2)\,(2^{-n}u_n - 1).$$

This leads to a value of

$$u_n = g\,1_{\cdot}2^{2N} + \ldots$$

This value differs from the one given in our paper (formula 6) by a factor 2. The value which you give agrees with ours. The error is therefore probably mine but I dont see now. The difference can not be due to the different ways in which mutation rate is defined in your and in our paper. As far as I can see the two definitions are equivalent. Both give mN as the mean number of mutations during one division cycle, where N is the number of bacteria at the beginning of the cycle.

Your variance also agrees with ours, formula 10.

It seems to me that your method and ours for the calculation of the moments are essentially the same. You compare the moments for n and for n+1 generations and then get the general expression by recurrence formulae, while we superimpose the Poisson distributions of each of the n generations. Our method has the advantage that we can make the cut off to eliminate the jackpots.

5. This whole argument was very enlightening to me. I had assumed, without much thinking, that the lack of synchronism in the divisions of the bacteria would entirely destroy the bias of the distribution in favor of powers of two. From your argument it seems that the bias may disappear only partially, since only the lack of synchronism in the terminal sections of the pedigrees matters. I am not clear in my mind as what the distribution would be if one retains perfect synchronism of the bacterial divisions but allows mutations to occur during any stage of the division cycle. Even if the mutations did occur at the divisions it might yet be true that the phenotypic appearance of resistance might occur at any stage during the division cycle. I think this question of whether the distribution is or is not biased in favor of powers of two is worth while following up theoretically and experimentally.

6. I do not understand the origin of the factor in front of the exponential in this equation. Also I am doubtful whether the result can be correct. Your argument, as I understand it, runs as follows: when the total number of viable bacteria has reached the value N the number of divisions which led to this number was

$$2(1-h)N/(2-h)(1-2h)$$

which is slightly greater than the corresponding number in the case of no deaths. Consequently there was more chance for mutation than in the standard case. Consequently p_0 is smaller than

in the standard case. But I do not see how you have taken account of the fact that a fraction of the mutants might have died out. Intuitively it seems to me that the deaths should not make any difference as long as the deaths occur with equal chance for normals and for mutants.

I am sorry that I have delayed so long writing this letter, and have been keeping your manuscript. When I came back there was here first the symposium and then a phage course for three weeks, and neither left sufficient leisure time. The symposium was very exciting, as you may have heard. A number of people thought they had indications of sex life in bacteria. If bacteria have sex it is entirely reasonable that it should be discovered now since now for the first time people are doing experiments with genetically marked strains. The most exciting experiments were some done at Yale in Tatums laboratory by a young fellow Lederberg. He first secured two double mutants of a strain of E.coli (X-ray induced). Each of the double mutants had two growth factor deficiencies. One mutant was deficient for A and B, say, and the other for C and D. Then he grew these two mutants together in broth. Then he plated the mixture out on basal medium and obtained a few "prototrophs" i.e. colonies of bacteria requiring no growth factor. He seemed to have done most of the obvious control experiments. He has since tried to do the same thing with our strain "B". He did secure two double deficient mutants, but did not get any prototrophs when growing them together.

Luria has been trying to do a similar experiment with mutants of the phage resistance type. He takes, say, B/1/2 and B/3/4 and grows them together and then tests to see whether he has any B/1/2/3/4. So far no luck.

With best regards

sincerely yours

M. Delbrück